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TRANSMITTAL OF PRIORITY DOCUMENT UNDER 35 USC § 119

Applicants hereby confirm their claim of priority under 35 USC § 119 from the following application(s):

- Sweden Application No. 0004244-0 filed November 20, 2000.

A certified copy of the application from which priority is claimed is submitted herewith.

Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: January 28, 2002

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NOVEL COMPOUNDS AND THEIR USE

Field of the invention

The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to processes for their preparation, as well as to the use of the compounds for the preparation of a medicament which particularly acts on the central nervous system.

Background of the invention

Many diseases of the central nervous system are influenced by the adrenergic, the dopaminergic, and the serotonergic neurotransmitter systems. For example, serotonin has been implicated in a number of diseases and conditions which originate in the central nervous system. A number of pharmacological and genetic experiments involving receptors for serotonin strongly implicate the 5-HT_{2c} receptor subtype in the regulation of food intake (Obes. Res. 1995, 3, Suppl. 4, 449S-462S). The 5-HT_{2c} receptor subtype is transcribed and expressed in hypothalamic structures associated with appetite regulation. It has been demonstrated that the non-specific 5-HT_{2c} receptor agonist *m*-chlorophenylpiperazine (mCPP), which has some preference for the 5-HT_{2c} receptor, causes weight loss in mice that express the normal 5-HT_{2c} receptor while the compound lacks activity in mice expressing the mutated inactive form of the 5-HT_{2c} receptor (Nature 1995, 374, 542-546). In a recent clinical study, a slight but sustained reduction in body weight was obtained after 2 weeks of treatment with mCPP in obese subjects (Psychopharmacology 1997, 133, 309-312). Weight reduction has also been reported from clinical studies with other "serotonergic" agents (see e.g. IDrugs 1998, 1, 456-470). For example, the 5-HT reuptake inhibitor fluoxetine and the 5-HT releasing agent/reuptake inhibitor dexfenfluramine have exhibited weight reduction in controlled studies. However, currently available drugs that increase serotonergic transmission appear to have only a moderate and, in some cases, transient effects on the body weight.

The 5-HT_{2c} receptor subtype has also been suggested to be involved in CNS disorders such as depression and anxiety (Exp. Opin. Invest. Drugs 1998, 7, 1587-1599; IDrugs, 1999, 2, 109-120).

The 5-HT_{2c} receptor subtype has further been suggested to be involved in urinary disorders such as urinary incontinence (IDrugs, 1999, 2, 109-120).

Compounds which have a selective effect on the 5-HT_{2c} receptor may therefore have a therapeutic potential in the treatment of disorders like those mentioned above. Of course, selectivity also reduces the potential for adverse effects mediated by other serotonin receptors.

Information disclosure

US-A-3,253,989 discloses the use of mCPP as an anorectic agent.

EP-A1-863 136 discloses azetidine and pyrrolidine derivatives which are selective 5-HT_{2c} receptor agonists having antidepressant activity and which can be used for treating or preventing serotonin-related diseases, including eating disorders and anxiety.

EP-A-657 426 discloses tricyclic pyrrole derivatives having activity on the 5-HT_{2c} receptor and which inter alia may be used for treating eating disorders.

EP-A-655 440 discloses 1-aminoethylindoles having activity on the 5-HT_{2c} receptor and which may be used for treating eating disorders.

EP-A-572 863 discloses pyrazinoindoles having activity on the 5-HT_{2c} receptor and which may be used for treating eating disorders.

J. Med. Chem. 1978, 21, 536-542 and US-A-4,081,542 disclose a series of piperazinylpyrazines having central serotonin-mimetic activity.

J. Med. Chem. 1981, 24, 93-101 discloses a series of piperazinylquinoxalines with central serotoninmimetic activity.

WO 00/12475 discloses indoline derivatives as 5-HT_{2b} and/or 5-HT_{2c} receptor ligands, especially for the treatment of obesity.

WO 00/12510 discloses pyrroloindoles, pyridoindoles and azepinoindoles as 5-HT_{2c} receptor agonists, particluarly for the treatment of obesity.

WO 00/12482 discloses indazole derivatives as selective, directly active 5-HT_{2c} receptor ligands, preferably 5-HT_{2c} receptor agonists, particularly for use as anti-obesity agents.

WO 00/12502 discloses pyrroloquinolines as 5-HT_{2c} receptor agonists, particularly for use as anti-obesity agents.

WO 00/35922 discloses 2,3,4,4*a*-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoxalin-5(6*H*)ones as $5HT_{2c}$ agonists, which may be used for the treatment of obesity.

WO 00/44737 discloses aminoalkylbenzofurans as $5\text{-}HT_{2c}$ agonists, which may be used for the treatment of obesity.

GB-B-1,457,005 discloses 1-piperazinyl-2-[2-(phenyl)ethenyl]-quinoxaline derivatives which exhibit anti-inflammatory activity.

Chem. Pharm. Bull. 1993, 41(10) 1832-1841 discloses $5\text{-}HT_3$ antagonists including 2-(4-methyl-1-piperazinyl)-4-phenoxyquinoxaline.

GB-B-1,440,722 discloses 2-(1'-piperazinyl)-quinoxaline compounds having pharmaceutical activity against depression.

WO 96/11920 discloses CNS-active pyridinylurea derivatives.

WO 95/01976 discloses indoline derivatives active as $5\text{-}HT_{2c}$ antagonists and of potential use in the treatment of CNS disorders.

WO 97/14689 discloses aryl-piperazine cyclic amine derivatives, which are selective $5\text{-}HT_{1d}$ receptor antagonists.

WO 98/42692 discloses piperazines derived from cyclic amines, which are selective antagonists of human $5\text{-}HT_{1a}$, $5\text{-}HT_{1d}$ and $5\text{-}HT_{1b}$ receptors.

GB-B-1,465,946 discloses substituted pyridazinyl, pyrimidinyl and pyridyl compounds which are active as β-receptor blocking agents.

EP-A-711757 discloses [3-(4-phenyl-piperazin-1-yl)propylamino]-pyridine, pyrimidine and benzene derivatives as α-adrenoceptor antagonists.

WO 99/03833 discloses aryl-piperazine derivatives, which are $5\text{-}HT_2$ antagonists and $5\text{-}HT_{1a}$ receptor agonists and therefore are useful as remedies or preventives for psychoneurosis.

WO 96/02525 discloses aryl-piperazine-derived piperazide derivatives having 5-HT receptor antagonistic activity.

WO 99/58490 disloses aryl-hydronaphthalen-alkane amines which may effectuate partial or complete blockage of serotonergic $5\text{-}HT_{2c}$ receptors in an organism.

Object of the invention

It is an object of the present invention to provide new compounds.

It is a further object of the invention to present compounds for use in therapy of a human being and animal.

A further object of the invention is use of compounds for the manufacture of a medicament for treating or preventing a serotonin related disease, especially related to the 5-HT_{2c} receptor.

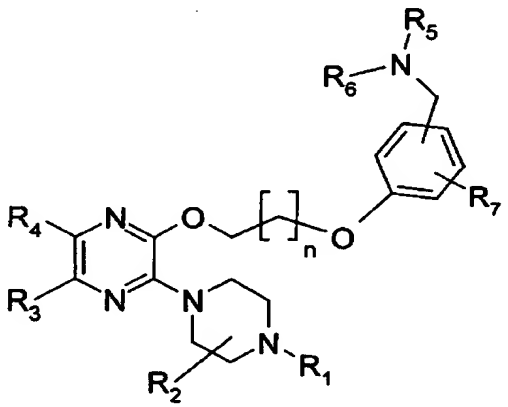
Yet another object of the invention is a pharmaceutical composition comprising compounds for use in therapy as an active ingredient.

Finally, an object of the invention is a method of treatment or prophylaxis of a serotonin related disease, especially a disease related to the 5-HT_{2c} receptor.

Summary of the invention

The objects of the invention are achieved by the compounds, the use of the compounds, the pharmaceutical composition and the method of treatment as claimed in the claims.

According to the invention novel compounds of the general formula (I) are provided:



(I)

wherein

R_1 is hydrogen or C_1-C_4-alkyl, C_{3-4}-alkenyl, C_{1-4}-acyl, C_{1-4}-alkoxycarbonyl, 2-hydroxyethyl, 2-cyanoethyl or tetrahydropyran-2-yl;

R_2 is hydrogen, C_{1-4}-alkyl, hydoxymethyl, C_{1-4}-alkoxymethyl or fluoromethyl;

R_3 and R_4 independently of each other are hydrogen, methyl, C_{1-4}-alkyl, aryl, heteroaryl wherein aryl and heteroaryl residues in turn may be substituted in one or more positions independently of each other by halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-

alkylthio, C_{1-4}-alkylsulphonyl, methanesulphonamido, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio or amino, methylamino, dimethylamino or acetamido;

or

R_3 and R_4 together with the carbon atoms to which they are bound form a 5- or 6-membered aromatic or heteroaromatic ring, which optionally is independently substituted in one or more positions by halogen, methyl, methoxy, methylthio, methylsulphonyl, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethylthio, amino, methylamino, dimethylamino or acetamido.

R_5 and R_6 independently of each other are hydrogen, C_1-C_4-alkoxy-C_2-C_4-alkyl, hydroxy-C_2-C_4-alkyl, C_1-C_6-alkyl, C_2-C_6-acyl, aryl, heteroaryl, aryl-C_1-C_2-alkyl, heteroaryl-C_1-C_2-alkyl, aryl-C_2-C_3-acyl, heteroaryl-C_2-C_3-acyl, and wherein any aryl or heteroaryl may be independently substituted in one or more positions by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{1-4}-acyl, C_{1-4}-alkylsulphonyl, cyano, nitro, hydroxy, C_{2-3}-alkenyl, C_{2-3}-alkynyl, fluoromethyl, trifluoromethyl, trifluoromethoxy, halogen, dimethylamino, methylamino;

or R_5 and R_6 together with the nitrogen atom to which they are bound form a saturated heterocyclic ring having 4-7 ring members which ring may contain an additional heteroatom and which may be substituted by methyl, oxo or hydroxy;

R_7 is hydrogen or a substituent selected from halogen, methyl, methoxy, ethoxy, or nitro;

and n = 1-3

and pharmaceutically acceptable salts, hydrates, geometrical isomers, tautomers, optical isomers, *N*-oxides and prodrug forms thereof.

In case the compounds of formula (I) can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.

In case the compounds of formula (I) contain groups which may exist in tautomeric forms, the invention comprises the tautomeric forms of the compounds as well as mixtures thereof.

In case the compounds of formula (I) can be in the form of geometrical isomers, the invention comprises the geometrical isomers as well as mixtures thereof.

In another aspect, the invention provides the compounds according to formula (I) above for use in therapy.

Still another aspect of the invention provides a pharmaceutical composition comprising a compound according to formula (I) above as the active ingredient, preferably together with a pharmaceutically acceptable carrier and, if desired, other pharmacologically active agents.

In yet another aspect, the invention provides a method for the treatment of a human or animal subject suffering from a serotonin-related disease, particularly 5-HT2 receptor-related, especially eating disorders, particularly obesity; memory disorders, schizophrenia, mood disorders, anxiety disorders, pain, sexual dysfunctions, epilepsy and urinary disorders.

Another aspect of the invention provides the use of the compounds according to formula (I) above for the manufacture of a medicament for the treatment of a serotonin-related disease, particularly 5-HT_2 receptor-related, especially eating disorders, particularly obesity; memory disorders; schizophrenia, mood disorders, anxiety disorders, pain, sexual dysfunctions, epilepsy and urinary disorders.

Finally a method for modulating 5HT2 receptor function is an aspect of the invention.

Detailed description of the invention

According to the present invention, a class of novel compounds have been developed which bind to the 5-HT_{2c} receptor (agonists and antagonists) and which therefore may be used for the treatment of serotonin-related disorders.

First, the various terms used, separately and in combinations, in the above definition of the compounds having the general formula (I) will be explained.

By "heteroatom" is meant nitrogen, oxygen, sulphur, and in heterocyclic rings (including heteroaromatic as well as saturated and partially saturated heterocyclic rings), also selenium.

The term "aryl" is intended to include aromatic rings (monocyclic or bicyclic) having from 6 to 10 ring carbon atoms, such as phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydronaphthyl (can be linked to the remainder of the molecule via a carbon atom in

any ring) and indanyl (can be linked to the remainder of the molecule via a carbon atom in any ring).

The term "heteroaryl" means a mono- or bicyclic aromatic ring system, only one ring need to be aromatic, and which can be linked to the remainder of the molecule via a carbon or nitrogen atom in any ring, and having from 5 to 10 ring atoms (mono- or bicyclic), in which one or more of the ring atoms are other than carbon, such as nitrogen, sulphur, oxygen and selenium. Examples of such heteroaryl rings are pyrrole, imidazole, thiophene, furan, thiazole, isothiazole, thiadiazole, oxazole, isoxazole, oxadiazole, pyridine, pyrazine, pyrimidine, pyridazine, pyrazole, triazole, tetrazole, chroman, isochroman, coumarin, quinoline, quinoxaline, isoquinoline, phthalazine, cinnoline, quinazoline, indole, isoindole, indoline, isoindoline, benzothiophene, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, benzoxazole, 2,1,3-benzoxadiazole, benzothiazole, 2,1,3-benzothiadiazole, 2,1,3-benzoselenadiazole, benzimidazole, indazole, 2,3-dihydro-1,4-benzodioxine, 1,3-benzodioxole, 1,2,3,4-tetrahydroquinoline, 3,4-dihydro-2*H*-1,4-benzoxazine, 1,5-naphthyridine, 1,8-naphthyridine, 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine, and 2,3-dihydro-1,4-benzoxathiine. If a bicyclic aryl or heteroaryl ring is substituted, it may be substituted in any ring.

C_{1-6}-alkyl, which may be straight or branched, is preferably C_{1-4}-alkyl. Exemplary alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, hexyl, and isohexyl.

C_{1-4}-alkoxy may be straight or branched. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy and *tert*-butoxy.

C_{2-4}-alkenyl may be straight or branched. Exemplary alkenyl groups include vinyl, 2-propenyl and 1-methyl-2-propenyl.

C_1-C_4-alkoxy-C_2-C_4-alkyl may be straight or branched. Exemplary groups include 2-(methoxy)ethyl, 3-methoxy-1-propyl, 4-ethoxy-1-butyl and the like.

Exemplary heteroaryl-C_2-C_3-acyl include nicotinoyl and 3-pyridinylacetyl and the like.

C_{2-6}-acyl may be saturated or unsaturated and is preferably C_{2-4}-acyl. Exemplary acyl groups include acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, butenoyl (e.g. 3-butenoyl), hexenoyl (e.g. 5-hexenoyl).

Halogen includes fluorine, chlorine and bromine.

Where it is stated above that aryl and heteroaryl residues may be substituted, this applies to aryl and heteroaryl *per se* as well as to any combined groups containing aryl or heteroaryl residues, such as heteroaryl- C_1-C_2-alkyl and aryl-C_2-C_3-acyl.

The term "*N*-oxides" means that one or more nitrogen atoms, when present in a compound, are in *N*-oxide form (N→O).

The term "prodrug forms" means a pharmacologically acceptable derivative, such as an ester or an amide, which derivative is biotransformed in the body to form the active drug. Reference is made to Goodman and Gilman's, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15.

"Pharmaceutically acceptable" means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like.

R_1 is preferably hydrogen or methyl.

R_1 may also serve as a nitrogen protecting group, and then R_1 is *t*-butoxycarbonyl (*t*-BOC), benzyl, or trityl, preferably trityl.

R_2 is preferably hydrogen or methyl (especially in the 2-position of the piperazine ring).

R_3 and R_4 are preferably (independently) hydrogen, halogen or methyl. When R_3 and R_4 form a ring together with the ring carbons to which they are bound, such a ring is preferably benzene (to give quinoxaline) or thiophene (to give thieno[3,4-b]pyrazine). When substituted, the rings are preferably mono- or (independently) disubstituted, such as by halogen or methyl.

When R_5 and R_6 form a saturated heterocyclic ring, exemplary rings are azetidine, pyrrolidine, piperazine, morpholine, thiomorpholine or piperidine.

R_7 may occupy any available position of the phenyl ring.

The group $-CH_2N(R_5)(R_6)$ may be attached to the *orto-*, *meta-*, or the *para* position of the phenyl ring, preferably the *meta* position.

n in formula (I) is 1-3 where n is the number of methylene groups. n is preferably 1, having the meaning that the two oxygen atoms in formula (I) are spaced between a $-CH_2CH_2-$ group;

Preferred compounds of the general formula (I) above are:

2-(1-Piperazinyl)-3-{2-[3-(4-morpholinylmethyl)phenoxy]ethoxy}pyrazine;

2-(1-Piperazinyl)-3-{2-[3-(1-pyrrolidinylmethyl)phenoxy]ethoxy}pyrazine;

2-(1-Piperazinyl)-3-{2-[3-(4-methyl-1-piperazinylmethyl)phenoxy]ethoxy}pyrazine;

2-(1-Piperazinyl)-3-{2-[3-{(2-methoxyethyl)amino}methyl)phenoxy]ethoxy}pyrazine;

2-(1-Piperazinyl)-3-{2-[3-{(isopropylamino)methyl}phenoxy]ethoxy}pyrazine,

and their pharmacologically acceptable salts and solvates.

As mentioned above, the compounds of the present invention are useful for the treatment (including prophylactic treatment) of serotonin-related disorders, especially 5-HT2 receptor-related, in a human being or in an animal (including e.g. pets), such as eating disorders, especially obesity; memory disorders, such as Alzheimer's disease; schizophrenia; mood disorders, including, but not restricted to, major depression and bipolar depression, including both mild and manic bipolar disorder, seasonal affective disorder (SAD); anxiety disorders, including situational anxiety, generalised anxiety disorder, primary anxiety disorders (panic disorders, phobias, obsessive-compulsive disorders, and post-traumatic stress disorders), and secondary anxiety disorders (for example anxiety associated with substance abuse); pain; sexual dysfunctions; epilepsy and urinary disorders, such as urinary incontinence.

The compounds of the present invention in labelled form, e.g. isotopically labelled, may be used as a diagnostic agent.

The compounds of the general formula (I) above may be prepared by, or in analogy with, conventional methods.

For example, as shown in Scheme 1, a compound of formula (I) may be prepared by first treating a compound of formula (II), wherein Hal is halogen and R_3 and R_4 are as defined above, with an appropriate piperazine of formula (III), wherein R_1 and R_2 have the same meaning as in formula (I) and where R_1 may be a suitable nitrogen protecting group, such as trityl, benzyl or *tert*-butoxycarbonyl, to provide a compound of formula (IV). The reaction is carried out in a solvent, such as, acetonitrile, dioxane, tetrahydrofuran (THF), *n*-butanol, *N,N*-dimethylformamide (DMF), or in a mixture of solvents such as DMF/dioxane, optionally in the presence of a base, such as K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOH, triethylamine, pyridine or the like, at 0-200 °C for 1-24 hours.

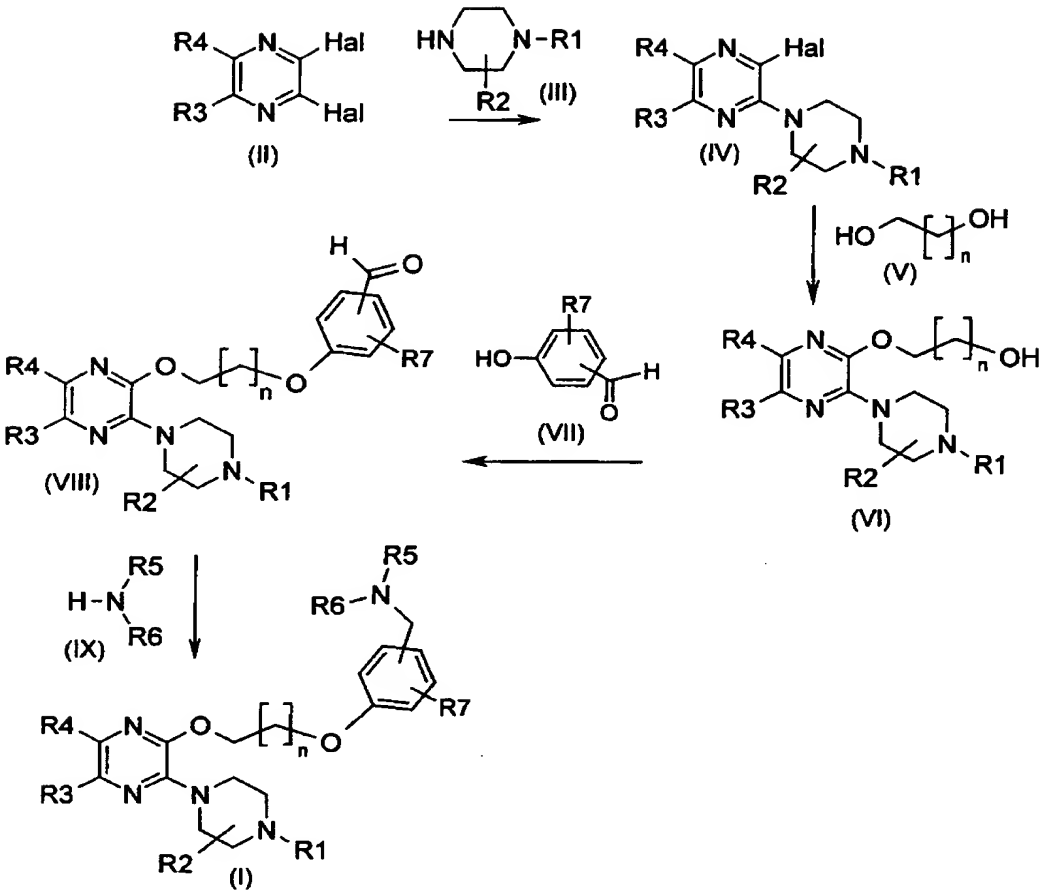
The compound of formula (IV) is reacted with a diol of formula (V), wherein *n* has the same meaning as in formula (I), to provide intermediate (VI). The reaction is carried out in a solvent, such as, dioxane, THF, DMF or pyridine, and the like, in the presence of a base such as K-*t*-BuO, Na-*t*-BuO, NaH or the like, at 0-150 °C for 1-24 hours.

Intermediate (VI) is reacted with a hydroxybenzaldehyde compound of formula (VII), wherein R_7 has the same meaning as in formula (I), to provide the aldehyde intermediate (VIII). The reaction may be carried out in the presence of diethyl azodicarboxylate (DEAD) or 1,1'-azobis(*N,N*-dimethylformamide) (cf. Tetrahedron Lett. 1995, 36, 3789-3792), preferably DEAD, and triphenylphosphine (PPh_3) in a solvent such as THF or dichloromethane (Mitsunobu reaction; see: Org. React. 1992, 42, 335-656.).

Subjecting intermediate (VIII) to a standard reductive alkylation procedure (such as described in J. Org. Chem. 1996, 61, 3849-3862), with an appropriate amine of formula (IX), wherein R_5 and R_6 have the same meaning as in formula (I), results in a compound of this invention (X).

When R_1 in formula (I) is a nitrogen protecting group as defined above, the subsequent *N*-deprotection may be performed under standard conditions, such as those described in Protective Groups in Organic Synthesis, John Wiley & Sons, 1991, to provide compounds of formula (I) wherein R_1 is hydrogen.

Scheme 1.



An obtained compound of formula (I) may be converted to another compound of formula (I) by methods well known in the art.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. A pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Examples of addition salt forming acids are maleic acid, fumaric acid, succinic acid, methanesulfonic acid, trifluoroacetic acid, acetic acid, oxalic acid, benzoic acid, hydrochloric acid, sulphuric acid, phosphoric acid, and the like.

The compounds of formula (I) may possess one or more chiral carbon atoms, and they may therefore be obtained in the form of optical isomers, e.g., as a pure

enantiomer, or as a mixture of enantiomers (racemate) or as a mixture containing diastereomers. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and may, for example, be achieved by fractional crystallization of salts with optically active (chiral) acids or by chromatographic separation on chiral columns.

In accordance with the present invention, the compounds of formula (I), in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of formula (I) in association with compatible pharmaceutically acceptable carrier materials, or diluents, as are well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous, subcutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, pills, capsules, powders, syrups, elixirs, dispersable granules, cachets, suppositories and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, sprays, e.g. a nasal spray, transdermal preparations, e.g. patches, and the like.

As mentioned above, the compounds of the invention may be used for the treatment of serotonin-related disorders in a human being or an animal, such as eating disorders, particularly obesity, memory disorders, schizophrenia, mood disorders, anxiety disorders, pain, sexual dysfunctions, epilepsy and urinary disorders. The compounds may also be useful for treating gastrointestinal disorders, such as gastrointestinal mobility disorders, e.g. irritable bowel syndrome (IBS), or glaucoma. The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the

metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

The invention will now be further illustrated by the following non-limiting Examples.

EXAMPLES

General:

NMR spectra were recorded on a Bruker Avance DPX 400 MHz spectrometer at 25 °C. Chemical shifts are given in ppm relative to tetramethylsilane. LCMS data were obtained using an HP1100 hplc system coupled to a Micromass platform LC mass spectrometer running MassLynx. Details of the hplc are: Column, Phenomenex C18 Luna, 30 x 46 mm at 40 ± 1 °C. Eluant gradient T= 0, 95% (0.1% formic acid in water) and 5% (0.1% formic acid in acetonitrile, then a linear gradient to T= 2.5 min, 5% (0.1% formic acid in water) and 95% (0.1% formic acid in acetonitrile), then a further 1 min at these conditions. Eluent flow rate was 2 mL/min. Detection was by UV diode array at window 210-400 nm. Alternate +ve and –ve ion APCI mass spectra were collected throughout the 3.5 min, scanning between 100 and 650 mass units. High resolution MS were obtained on a Micromass LCT spectrometer. Developing solvents for TLC on silica were di-isopropylether or ethyl acetate/light petroleum mixtures.

EXAMPLE 1

2-(1-Piperazinyl)-3-{2-[3-(4-morpholinylmethyl)phenoxy]ethoxy}pyrazine.

Step 1: 2-Chloro-3-(4-*tert*-butoxycarbonyl-1-piperazinyl)pyrazine.

A mixture of *N*-Boc-piperazine (11.47 g, 61.5 mmol), K_2CO_3 (8.5 g, 61 mmol) and 2,3-dichloropyrazine (9.20 g, 61.7 mmol) in acetonitrile (100 mL) was stirred at 100 °C for 40 h. The reaction mixture was concentrated, dissolved in toluene, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica

gel using toluene/EtOAc (7:3) as eluent to give 18.3 g (100%) of the title product. HRMS *m/z* calcd for $C_{13}H_{19}N_4O_2$ $(M)^+$ 298.1197, found 298.1206.

Step 2: 2-[3-(4-*tert*-Butoxycarbonyl-1-piperazinyl)-2-pyrazinyloxy]ethanol.

KO-*t*-Bu (9.92 g, 103 mmol) was added to a mixture of the product obtained in step 1 (18.14 g, 60.7 mmol) and ethylene glycol (25 mL, 448 mmol) in pyridine (125 mL) at 85 °C. The reaction mixture was stirred for 15 h and then poured into ice-water and extracted with toluene. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel using toluene/EtOAc (1:1) as eluent to give 16.9 g (85%) of the title product. HRMS *m/z* calcd for $C_{15}H_{24}N_4O_4$ $(M)^+$ 324.1798, found 324.1784.

Step 3: *tert*-Butyl 4-{3-[2-(3-formylphenoxy)ethoxy]-2-pyrazinyl}-1-piperazinecarboxylate.

A solution of the compound obtained in step 2 above (1.5 g, 4.7 mmol) in dry tetrahydrofuran (THF; 10 mL) was treated with 3-hydroxybenzaldehyde (0.74 g, 6.06 mmol) and triphenylphosphine (1.59 g, 6.06 mmol). This solution was stirred at room temperature then treated with diethyl azodicarboxylate (0.96 mL, 6.06 mmol) in dry THF (5 mL). After 1 hr, TLC indicated some remaining 2-[3-(4-*tert*-butoxycarbonyl-1-piperazinyl)-2-pyrazinyloxy]ethanol. The reaction was heated at reflux under nitrogen for 5 h, then left to cool to room temperature overnight. TLC again showed unreacted starter. The mixture was treated with further triphenylphosphine (0.80 g, 3.03 mmol), diethyl azodicarboxylate (0.5 mL, 3.03 mmol) and 3-hydroxybenzaldehyde (0.40 g, 3.03 mmol), then stirred at RT for a further 3 hrs (reaction complete by TLC). The volatiles were removed *in vacuo* and the residue was purified by flash column on silica gel, eluting with petroleum ether/ethyl acetate (2:1). This furnished 0.33 g (16%) of the title product as a colourless oil. ^1H NMR ($CDCl_3$) δ 1.5 (s, 9H); 3.5 (bs, 8H), 4.45 (m, 2H); 4.75 (m, 2H); 7.2 (d, 1H); 7.45 (s, 1H); 7.5 (m, 2H); 7.6 (s, 1H); 7.75 (s, 1H).

Step 4: *tert*-Butyl 4-(3-{2-[3-(4-morpholinylmethyl)phenoxy]ethoxy}-2-pyrazinyl)-1-piperazinecarboxylate.

A stirred solution of the aldehyde from step 3 above (71.2 mg, 0.166 mmol) in 1,2-dichloroethane (5 mL) was treated with morpholine (19 mg, 0.22 mmol), 3Å molecular sieves and sodium triacetoxyborohydride (52 mg, 0.25 mmol). The mixture was stirred at room temperature for 5 h (TLC monitoring). The solution was filtered and the filtrate was treated with an excess of saturated aqueous sodium bicarbonate. The ether extracts were separated and dried over magnesium sulfate. The mixture was filtered and solvent was removed *in vacuo* to give 54 mg (65%) of the title product as a yellow oil. Pure by NMR. ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 9H); 2.35 (m, 4H); 3.4 (m, 10H); 3.65 (m, 4H); 4.3 (m, 2H); 4.65 (m, 2H); 6.75 (d, 1H); 6.9 (m, 2H); 7.2 (t, 1H); 7.5 (s, 1H); 7.7 (s, 1H).

Step 5: 2-(1-Piperazinyl)-3-{2-[3-(4-morpholinylmethyl)phenoxy]ethoxy}pyrazine. The product from step 4 above (54 mg, 0.11 mmol) was dissolved in dry ether (20 mL), stirred at room temperature and treated with hydrogen chloride in ether (~6 M; 5 mL). The resulting white suspension was stirred for 2 h, then quickly filtered off. The hydrochloride salt (hygroscopic), was dissolved in water and neutralized with sodium carbonate. The free base was extracted into dichloromethane. The organic layers were dried magnesium sulfat, filtered, and concentrated *in vacuo* to furnish 13 mg (29%) of the title product as a pale yellow oil. LS/MS purity 100%. ^{1}H NMR ($CDCl_3$) δ 1.8 (b, 1H); 2.45 (m, 4H); 2.95 (m, 4H); 3.45 (s, 2H); 3.55 (m, 4H); 3.7 (m, 4H); 4.35 (t, 2H); 4.7 (t, 2H); 6.85 (d,1H); 6.95 (m, 2H); 7.25 (t, 1H); 7.55 (s, 1H); 7.75 (s, 1H).

The following compounds were prepared analogously from *tert*-butyl 4-{3-[2-(3-formylphenoxy)ethoxy]-2-pyrazinyl}-1-piperazinecarboxylate (obtained in example 1, step 3 and the requisite amine.

EXAMPLE 2

2-(1-Piperazinyl)-3-{2-[3-(1-pyrrolidinylmethyl)phenoxy]ethoxy}pyrazine. Yield 31%. LS/MS purity 100%. ^{1}H NMR ($CDCl_3$) δ 1.7 (m, 4H); 2.45 (m, 4H); 2.9 (m, 4H); 3.4 (m, 4H); 3.5 (s, 2H); 4.3 (m, 2H); 4.6 (m, 2H); 6.7 (d, 1H); 6.85 (m, 2H); 7.15 (t, 1H); 7.45 (s, 1H); 7.7 (s, 1H).

EXAMPLE 3

2-(1-Piperazinyl)-3-{2-[3-(4-methyl-1-piperazinylmethyl)phenoxy]ethoxy}pyrazine.

Yield 56%. LS/MS purity 100%. ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H); 2.35 (b, 9H); 2.85 (m, 4H); 3.35 (m, 6H); 4.2 (m, 2H); 4.55 (m, 2H); 6.7 (d, 1H); 6.8 (m, 2H); 7.1 (t, 1H); 7.4 (s, 1H); 7.6 (s, 1H).

EXAMPLE 4

2-(1-Piperazinyl)-3-{2-[3-{(2-methoxyethyl)amino}methyl)phenoxy]ethoxy}pyrazine.

Yield 37%. LS/MS purity 100%. ^{1}H NMR ($CDCl_3$) δ 2.8 (t, 2H); 3.05 (m, 6H); 3.35 (s, 3H); 3.6 (m, 6H); 3.8 (s, 2H); 4.35 (m, 2H); 4.7 (m, 2H); 6.8 (d, 1H); 6.95 (d, 2H); 7.25 (t, 1H); 7.55 (s, 1H); 7.8 (s, 1H).

EXAMPLE 5

2-(1-Piperazinyl)-3-{2-[3-{(isopropylamino)methyl}phenoxy]ethoxy}pyrazine.

Yield 60%. LS/MS purity 100%. ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 6H); 1.85 (b, 1H); 2.85 (m, 1H); 3.0 (m, 4H); 3.5 (m, 4H); 3.8 (s, 2H); 4.35 (m, 2H); 4.7 (m, 2H); 6.8 (d, 1H); 6.9 (m, 2H); 7.2 (t, 1H); 7.5 (s, 1H); 7.75 (s, 1H).

EXAMPLE 6

***N*-(3-Methoxyphenyl)-N-[3-(2-{[3-(1-piperazinyl)-2-pyrazinyl]oxy}ethoxy)benzyl]amine.**

LC/MS purity 100%.

EXAMPLE 7

2-{[3-(2-{[3-(1-Piperazinyl)-2-pyrazinyl]oxy}ethoxy)benzyl]amino}ethanol.

LC/MS purity 97%.

PREPARATION OF PHARMACEUTICAL COMPOSITIONS

EXAMPLE: Preparation of tablets

	Ingredients	mg/tablet
1.	Active compound	10.0
2.	Cellulose, microcrystalline	57.0
3.	Calcium hydrogen phosphate	15.0
4.	Sodium starch glycolate	5.0
5.	Silicon dioxide, colloidal	0.25
6.	Magnesium stearate	0.75

The active ingredient 1 is mixed with ingredients 2, 3, 4 and 5 for about 10 minutes. The magnesium stearate is then added, and the resultant mixture is mixed for about 5 minutes and compressed into tablet form with or without film-coating.

Pharmacological tests

The ability of a compound of the invention to bind or act at specific 5-HT receptor subtypes can be determined using *in vitro* and *in vivo* assays known in the art. The biological activity of compounds prepared in the Examples was tested using different tests.

Affinity assay

The 5-HT_{2c} receptor affinity of compounds in the Examples was determined in competition experiments, where the ability of each compound in serial dilution to displace ^{3}H-labelled 5-HT, bound to membranes prepared from a transfected HEK293 cell line stably expressing the human 5-HT_{2c} receptor protein, was monitored by Scintillation Proximity Assay technology. Non-specific binding was defined using 5 μM mianserin. Results obtained for exemplary compounds of the invention are illustrated in Table 1 below. Typically, the $5HT_{2C}$ receptor affinity values (K_i, nM) were in the range of 1 nM to 1500 nM, preferably 1 nM to 100 nM.

Table 1

Compound	Ki (nM)
Example 1	18
Example 5	3

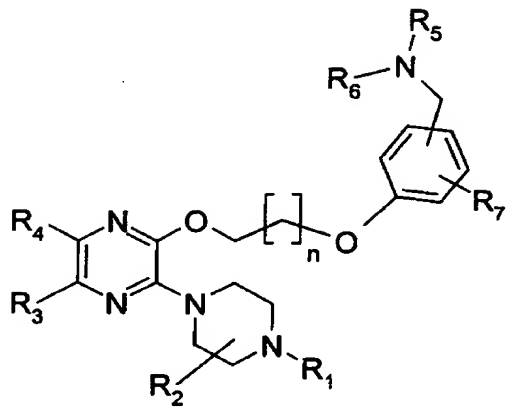
Efficacy assay

The agonist efficacy at the 5-HT_{2c} receptor of the compounds in the Examples was determined by the ability of each compound to mobilise intracellular calcium in transfected HEK293 cells, stably expressing the human 5-HT_{2c} receptor protein, using the calcium-chelating fluorescent dye FLUO-3 (Sigma, St. Louis, MO, U.S.A.).

Typically, the maximum responses of 5-HT_{2c} agonists were in the range of 15-100% relative to the maximum response of 5-HT (serotonin) at a concentration of 1 μM.

Claims

1. A compound of the general formula (I):



(I)

wherein

R_1 is hydrogen or C_1-C_4 alkyl, C_{3-4}-alkenyl, C_{1-4}-acyl, C_{1-4}-alkoxycarbonyl, 2-hydroxyethyl, 2-cyanoethyl or tetrahydropyran-2-yl;

R_2 is hydrogen, C_{1-4}-alkyl, hydroxymethyl, C_{1-4}-alkoxymethyl or fluoromethyl;

R_3 and R_4 independently of each other are hydrogen, methyl, C_{1-4}-alkyl, aryl, heteroaryl wherein aryl and heteroaryl residues in turn may be substituted in one or more positions independently of each other by halogen, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{1-4}-alkylsulphonyl, methanesulphonamido, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio or amino, methylamino, dimethylamino or acetamido;

or

R_3 and R_4 together with the carbon atoms to which they are bound form a 5- or 6-membered aromatic or heteroaromatic ring, which optionally is independently substituted in one or more positions by halogen, methyl, methoxy, methylthio, methylsulphonyl, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethylthio, amino, methylamino, dimethylamino or acetamido;

R_5 and R_6 independently of each other are hydrogen, C_1-C_4-alkoxy-C_2-C_4-alkyl, hydroxy-C_2-C_4-alkyl, C_1-C_6-alkyl, C_2-C_6-acyl, aryl, heterocyclyl, aryl-C_1-C_2-alkyl, heteroaryl-C_1-C_2-alkyl, aryl-C_2-C_3-acyl, heteroaryl-C_2-C_3-acyl, and wherein any aryl or heteroaryl may be independently substituted in one or more positions by C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-alkylthio, C_{1-4}-acyl, C_{1-4}-alkylsulphonyl, cyano, nitro, hydroxy, C_{2-3}-alkenyl, C_{2-3}-alkynyl, fluoromethyl, trifluoromethyl, trifluoromethoxy, halogen, dimethylamino, methylamino; or

R_5 and R_6 together with the nitrogen atom to which they are bound form a saturated heterocyclic ring having 4-7 ring members which ring may contain an additional heteroatom and which may be substituted by methyl, oxo or hydroxy;

R_7 is hydrogen or a substituent selected from halogen, methyl, methoxy, ethoxy, or nitro;

n = 1 – 3;

and pharmaceutically acceptable salts, hydrates, geometrical isomers, tautomers, optical isomers, *N*-oxides and prodrug forms thereof.

2. A compound according to claim 1, wherein R_1 is hydrogen or methyl.

3. A compound according to claim 1 or 2, wherein R_2 is hydrogen or methyl.

4. A compound according to claims 1 - 3, wherein

R_3 and R_4 (independently) are hydrogen, halogen or methyl; or when

R_3 and R_4 form a ring together with the ring carbons to which they are bound the ring is benzene or thiophene and when the rings are substituted they are mono or disubstituted.

5. A compound according to claims 1 – 4, wherein the group $-CH_2N(R_5)(R_6)$ is attached to the *meta*-position of the phenyl ring.

6. A compound according to any of claims 1 – 5, wherein

R_5 and R_6 together with the nitrogen atom to which they are bound form a ring selected from azetidine, pyrrolidine, piperazine, morpholine, thiomorpholine or piperidine.

7. A compound accordning to claims 1- 6, wherein R_7 is hydrogen.

8. A compound according to claims 1- 7, wherein n = 1.

9. A compound according to any of claims 1 – 8, selected from
2-(1-Piperazinyl)-3-{2-[3-(4-morpholinylmethyl)phenoxy]ethoxy}pyrazine;
2-(1-Piperazinyl)-3-{2-[3-(1-pyrrolidinylmethyl)phenoxy]ethoxy}pyrazine;
2-(1-Piperazinyl)-3-{2-[3-(4-methyl-1-piperazinylmethyl)phenoxy]ethoxy}pyrazine;
2-(1-Piperazinyl)-3-{2-[3-{(2-methoxyethyl)amino}methyl)phenoxy]ethoxy}pyrazine;
2-(1-Piperazinyl)-3-{2-[3-{(isopropylamino)methyl}phenoxy]ethoxy}pyrazine.

10. A compound according to any one of claims 1 to 9 for use in therapy of a human being or an animal.

11. A compound according to claim 10, wherein the therapy is directed towards prophylaxis or treatment of a serotonin-related disease.

12. A compound according to claim 11, wherein the serotonin-related disease is related to the 5-HT_2 receptor.

13. A compound according to claim 12, wherein the serotonin-related disease is related to the 5-HT_{2c} receptor.

14. A compound according to claim 11, wherein the serotonin-related disease is selected from eating disorders.

15. A compound according to claim 14, wherein the eating disorder is obesity.

16. A compound according to claim 11, wherein the serotonin-related disease is selected from memory disorders.

17. A compound according to claim 11, wherein the serotonin-related disease is selected from mood disorders.

18. A compound according to claim 11, wherein the serotonin-related disease is selected from anxiety disorders.

19. A compound according to claim 11, wherein the serotonin-related disease is selected from sexual dysfunctions, epilepsy and urinary disorders.

20. A compound according to claim 11, wherein the serotonin-related disease is pain.

21. A compound according to claim 11, wherein the serotonin-related disease is schizophrenia.

22. Use of a compound according to any one of claims 1 to 9 for the manufacture of a medicament for treating or preventing a serotonin-related disease.

23. Use according to claim 22 for treating or preventing a 5-HT_2 receptor related disease.

24. Use according to claim 23 for treating or preventing a $5HT_{2c}$ receptor related disease.

25. Use according to claim 22, wherein the serotonin-relateded disease is selected from eating disorders, memory disorders, schizophrenia, mood disorders, anxiety disorders, pain, sexual dysfunctions, epilepsy and urinary disorders.

26. Use according to claim 25 wherein the eating disorder is obesity.

27. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 as an active ingredient, together with a pharmacologically and pharmaceutically acceptable carrier.

28. A method for the prophylaxis or treatment of a serotonin-related disease in a human being or in an animal, which method comprises administering an effective amount of a compound according to any one of claims 1 to 9 to a subject suffering from said disease.

29. A method according to claim 28 wherein said disease is a 5-HT_2 receptor-related disease.

30. A method according to claim 29 wherein said disease is a 5-HT_{2c} receptor-related disease.

31. A method according to claim 29 wherein said disease is selected from eating disorders, memory disorders, schizophrenia, mood disorders, anxiety disorders, pain, sexual dysfunctions, epilepsy and urinary disorders.

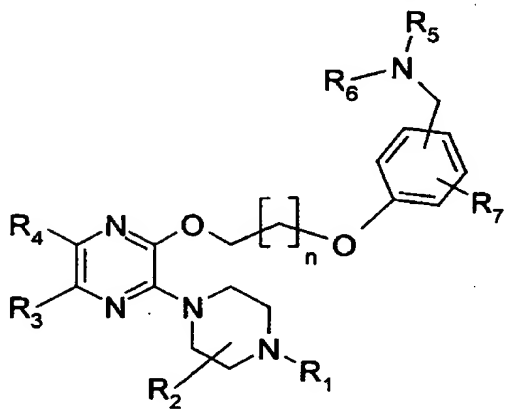
32. A method according to claim 31 wherein the eating disorder is obesity.

33. A method for modulating 5HT2 receptor function, comprising contacting the receptor with an effective inhibitory amount of a compound according to any of claims 1 to 9.

34. A method according to claim 33 for modulating the $5HT_{2c}$ receptor function.

ABSTRACT

The invention relates to compounds of the general formula (I)



(I)

wherein

R_1 is hydrogen or C_1-C_4 alkyl, C_{3-4}-alkenyl, C_{1-4}-acyl, C_{1-4}-alkoxycarbonyl, 2-hydroxyethyl, 2-cyanoethyl or tetrahydropyran-2-yl;

R_2 is hydrogen, C_{1-4}-alkyl, hydroxymethyl, C_{1-4}-alkoxymethyl or fluoromethyl;

R_3, R_4, R_5, R_6 and R_7 are as defined in the claims, and n is 1 – 3

and pharmaceutically acceptable salts, hydrates, geometrical isomers, tautomers, optical isomers, *N*-oxides and prodrug forms thereof.

Further inclueded are the compounds for use in serotonin related therapy and for the manufacture of a medicament and method of treatment as well as pharmaceutical compositions thereof.